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EDITORIAL COMMENT

Is There Anyone Left With a Normal Electrocardiogram?*

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The malignant early repolarization (ER) and Brugada syndromes (BS) are viewed as separate disorders sharing pathophysiological characteristics (1,2). Having said that, a clear "détente" between the 2 has prevailed: J waves, particularly when followed by a horizontal ST-segment (3), are the hallmark of ER, although only when present in the inferior and/or lateral leads (4). By contrast, only the presence of coved "type-I" ST-segment elevation is considered diagnostic of BS and only when present in the right precordial (V_1 to V_3) leads (5). Specifically, to launch the malignant ER as a novel form of idiopathic ventricular fibrillation (VF) not to be confused with BS, Haissaguerre et al. (6) scrutinized the inferior, lateral, and anterolateral leads for the presence of J waves while intentionally avoiding the right precordial leads. Every subsequent study confirming the association of J waves with idiopathic VF (4) adopted the same approach, deliberately neglecting leads V_1 to V_3.

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In this issue of the *Journal*, Kamakura et al. (7) take a fresh look at ER by reporting on the significance of J waves in V_1 to V_3, literally "trespassing into Brugada territory." They studied 84 patients with idiopathic VF, including 40 with BS, 13 with idiopathic VF with normal electrocardiogram (ECG), and 31 with ER (7). The last group was subdivided into 2: 19 patients had "classic early repolarization" with J waves restricted to the inferolateral leads, whereas the remaining 12 had J waves both in the inferolateral and the right precordial leads (7). This latter group, with "early repolarization in Brugada territory," represents a new category of patients, hitherto ignored. Because none of them developed a type I Brugada pattern when challenged with a sodium channel blocker (7), patients with ER in Brugada territory cannot be categorized as BS by contemporaneous criteria (5). Nonetheless, patients with abnormal right precordial repolarization (either in the form of right precordial ER or with frank type I Brugada pattern) shared important characteristics: spontaneous VF predominantly during sleep; and high risk for spontaneous VF recurrence (7).

This is not the first challenge to the credence maintaining that the type I Brugada ECG is the only right precordial risk indicator for cardiac arrest. A previous Japanese study (8) showed that the risk for spontaneous VF among patients with type II or type III Brugada pattern (also termed "non-type I Brugada pattern") was similar to that of patients with coved type I. Of note, 8% of the patients with non-type I Brugada pattern in that study (8) also had J waves in the inferolateral leads, and for those patients, the VF risk was twice as high. Thus, whether patients with inferolateral ER are noted to have right precordial J waves (as in the present study) (7) or whether patients with "non-type I Brugada are noted to have inferolateral J waves" (as in the aforementioned study) (8), having J waves in 2 territories portends a higher risk.

And the plot thickens: Rollin et al. (9) recently reported that 9% of patients with classic BS also have type I, coved ST-segment elevation, in at least 1 limb lead. Here, too, having a type I Brugada pattern in 2 territories was associated with a 5-fold increase in the risk for spontaneous VF (9). As discussed elsewhere (10), the emerging picture is that a greater "Brugada burden," manifesting as a type I Brugada pattern that is more severe (with higher ST-segment elevation), more frequent (observed in more ECGs recorded over time), or more widespread (observed in more leads), is a marker of higher risk.

As more and more variant ECG abnormalities are recognized to be associated with a higher arrhythmic-risk, the naive reader might conclude that almost everybody has some form of ECG abnormality and that these individuals are about to drop dead! An exaggeration? Well…consider the following. First, QTc values as short as 440 ms might be seen in patients with genetically confirmed long QT syndrome, whereas at least 1 patient with well-characterized short QT syndrome has had a QTc interval as long as 432 ms (11). Because these values, reflecting "short" or "long," represent the 60th and the 80th percentiles of the QTc interval in the healthy population (12), the inevitable conclusion is that only 20% of healthy individuals have unequivocally normal QT. Second, in population-based studies, as many as 9% of unselected adults have the "malignant form of early repolarization" (J waves with horizontal ST-segment), and these individuals are at increased risk of dying suddenly (3). Third, although the type I Brugada ECG is found in only 1 in 2,000 individuals (13), our data suggest that this pattern will be identified 20 times more frequently if only the ECG screening is performed at the time of fever (14). We must now add to these intimidating numbers the entity of "right-precordial J waves not meeting Brugada syndrome criteria yet associated with VF," as described here by Kamakura et al. (7). Although Kamakura did not include a control group (7),

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others suggest that >2% of apparently healthy subjects have type II to III Brugada pattern (13), and many more will have some form of J-point elevation in the right precordial leads. Individuals with a perfect ECG might soon prove hard to find, by these accounts.

The concept of "J waves in Brugada territory" has important implications. Electrophysiologists are already being consulted about the risk for arrhythmic death in young individuals who are asymptomatic but have prominent J waves. This "fear of J waves" (2) is likely to worsen once we start counting J waves in the right precordial leads. To keep matters in the proper perspective, it is important to remember the following points. First, the study by Kamakura et al. (7) included only VF survivors; the heightened risk of patients with J waves in 2 territories should not be extrapolated to asymptomatic individuals, who invariably have better prognosis. In the previous Japanese study (8) that did include asymptomatic individuals, long-term risk was driven primarily by the presence of symptoms: none of the initially asymptomatic individuals with non-type I Brugada pattern developed arrhythmias during a 4-year follow-up, regardless of the number of leads reflecting this phenomenon (8). Second, in the Rollin study (9), the risk for developing VF among asymptomatic individuals with type I Brugada in 2 lead territories reached 13% at 5 years, but this event rate requires confirmation, because it was based on only 2 cases. Third, the risk of idiopathic VF among asymptomatic individuals with "malignant early repolarization" (3) is estimated at only 1 in 3,000. Although high in relative terms (i.e., in comparison with the general population), the risk is low in absolute terms. Thus, the message that we ought to be delivering must be calming. Things are not as bad as they might seem for the asymptomatic individual with J waves.

Finally, the concept of "J waves in Brugada territory" also has important implications for individuals in need of medications that block the cardiac sodium channel (15). Asymptomatic individuals who have non-type I ST-segment elevation in V_1 to V_3 have an excellent long-term prognosis even if their ECG pattern converts to type I when challenged with a sodium channel blocker, even if they also have inducible VF during electrophysiological studies (16). The caveat to this reassuring statement is that individuals with drug-induced type I Brugada ECG will do well in the absence of drugs. Common sense dictates that such patients should vigilantly avoid treatment with any sodium channel blocker. Accumulating data suggest that the drug-induced Brugada syndrome is as important as the better-known drug-induced long QT syndrome (17). Interestingly, patients who developed drug-induced torsade de pointes might be identified through a drug challenge with a potassium channel blocker (18). Whether individuals with J waves should undergo a drug challenge with a sodium channel blocker to make sure they do not develop a type I Brugada pattern, before they receive potentially Brugadogenic medications (such as antipsychotic medications) for long-term use, is a thought that needs to be considered.

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REFERENCES

1. Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm 2010;7:549–58.
2. Viskin S. Idiopathic ventricular fibrillation, "Le Syndrome d'Haissaguerre" and the fear of J waves. J Am Coll Cardiol 2009;53:620–2.
3. Adler A, Rosso R, Viskin D, Halkin A, Viskin S. State of the art: what do we know about the "malignant form" of early repolarization? J Am Coll Cardiol 2013;62:863–8.
4. Viskin S, Rosso R, Halkin A. Making sense of early repolarization. Heart Rhythm 2012;9:566–8.
5. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference. Heart Rhythm 2005;2:429–40.
6. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016–23.
7. Kamakura T, Kawata H, Nakajima I, et al. Significance of non-type I anterior early repolarization in patients with inferolateral early repolarization syndrome. J Am Coll Cardiol 2013;62:1610–8.
8. Kamakura S, Ohe T, Nakazawa K, et al. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol 2009;2:495–503.
9. Rollin A, Sacher F, Gourraud JB, et al. Prevalence, characteristics, and prognosis role of type 1 ST elevation in the peripheral ECG leads in patients with Brugada syndrome. Heart Rhythm 2013;10:1012–8.
10. Viskin S, Adler A, Rosso R. Brugada burden in Brugada syndrome: the way to go in risk stratification? Heart Rhythm 2013;10:1019–20.
11. Templin C, Ghadri JR, Rougier JS, et al. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). Eur Heart J 2011;32:1077–88.
12. Allan WC, Timothy K, Vincent GM, Palomaki GE, Neveux LM, Haddow JE. Long QT syndrome in children: the value of rate corrected QT interval and DNA analysis as screening tests in the general population. J Med Screen 2001;8:173–7.
13. Mizusawa Y, Wilde AA. Brugada syndrome. Circ Arrhythm Electrophysiol 2012;5:606–16.
14. Adler A, Topaz G, Heller K, et al. Fever-induced type I Brugada pattern: how common is it and what does this mean? Heart Rhythm 2013;62:863–8.
15. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;6:1335–41.
16. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012;59:37–45.
17. Bardai A, Amin AS, Blom MT, et al. Sudden cardiac arrest associated with use of a non-cardiac drug that reduces cardiac excitability: evidence from bench, bedside, and community. Eur Heart J 2013;34:1506–16.
18. Kaab S, Hinterseer M, Nabauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome—a case-control pilot study using i.v. sotalol. Eur Heart J 2003;24:649–57.

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